CHEMISTRY LETTERS, pp. 19-22, 1976. Published by the Chemical Society of Japan

A CONVENIENT METHOD FOR N^4-BENZOYLATION OF CYTIDYLIC AND DEOXYCYTIDYLIC ACIDS BY MEANS OF O-ETHYL S-BENZOYLDITHIOCARBONATE

Hiroshi TAKAKU, Yoshifusa SHIMADA, and Yoshiaki MORITA
Laboratory of Organic Chemistry, Chiba Institute of Technology
Narashino-shi, Chiba 275
Tsujiaki HATA
Laboratory of Chemistry for Natural Products, Faculty of Science,
Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

O-Ethyl S-benzoyldithiocarbonate was found to be a useful reagent for benzoylation of the 4-amino groups of cytidine 5'-phosphate and deoxycytidine 5'-phosphate. By use of the reagent, N^4-benzoylcytidine and N^4-benzoyldeoxycytidine were also obtained in high yields.

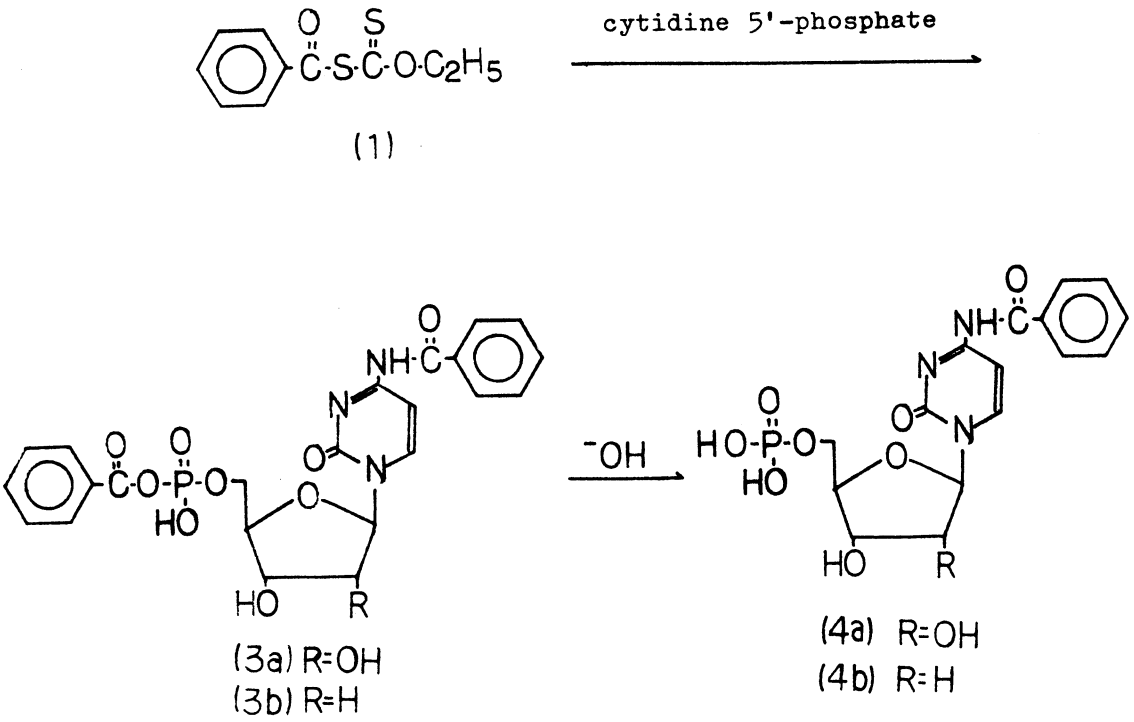
4-Amino group of cytidine is a highly sensitive amino group toward electrophiles. Therefore, several protecting groups for the amino group of cytidine were proposed.[1] Among these protecting groups benzoyl and anisoyl groups are most frequently used because of the stability and the suitability of the removal condition. There have been reported selective benzoylating reagents for protection of 4-amino group of cytidine. However, little is known for cytidylic and deoxycytidylic acids since the nucleotides do not easily dissolve in organic solvents.

In this communication, we wish to report the N^4-benzoylation of cytidylic and deoxycytidylic acids by means of O-ethyl S-benzoyldithiocarbonate.

The benzoylating reagent, O-ethyl S-benzoyldithiocarbonate (1), was prepared in 90% yield by a modification of the procedure of Nair.[2,3]

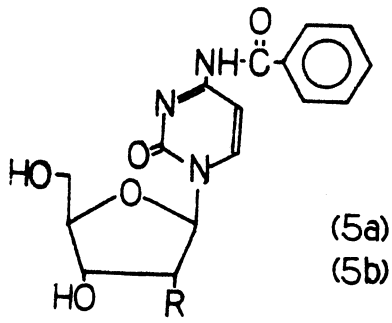
Cytidine 5'-phosphate (0.1 mmole) was treated with 1 (0.5 mmole) in dry dimethylformamide (DMF) (5 ml) at room temperature for 4 hr. N^4-Benzoylcytidine 5'-phosphoric benzoic anhydride (3) was formed. It was detected by paper electrophoresis developed by 0.05 M phosphate buffer, pH 8.0. Then the mixture was concentrated in vacuo. The residue was treated with 2N-sodium hydroxide at room temperature for 20 min. Dowex 50W-X2 (pyridinium form) was added for neutralization. After removal of the resin by filtration, the filtrate was further passed through a column of Dowex 50W-X2 (pyridinium form). The eluate was washed with ether and concentrated to dryness. N^4-Benzoylcytidine 5'-phosphate (4a) was obtained in 83% yield as an oily substance [$\lambda_{max}^{H_2O}$ 303, 259 (ε18,800); $\lambda_{min}^{H_2O}$ 286, 234 nm, Rf; 0.35 (A)[4]], which was homogeneous on paper chromatography.

In the same manner, N^4-benzoyldeoxycytidine 5'-phosphate (4b) was obtained in 80% yield [$\lambda_{max}^{H_2O}$ 304, 259 (ε18,800); $\lambda_{min}^{H_2O}$ 283, 233 nm, Rf; 0.42 (A)[4]].



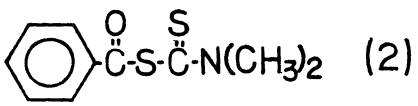
Further, the benzoylation of cytidine and deoxycytidine by means of 1 was attemped. When cytidine (1 mmole) was treated with 1 (5 mmole) in dry pyridine (10 ml) at room temperature for 4 hr, N^4-benzoylcytidine (5a), mp. 220 °C (lit.[5] 219 °C), was obtained in 82% yield [λ_{max}^{EtOH} 303, 259 (ε 22,300); λ_{min}^{EtOH} 286, 234 nm, Rf; 0.67 (B)[4]].

In a similar manner, N^4-benzoyldeoxycytidine (5b), mp. 204-205 °C (lit.[6] 205-207 °C), was obtained in 86% yield [λ_{max}^{EtOH} 304, 259 (ε 20,900); λ_{min}^{EtOH} 285, 232 nm, Rf; 0.77 (B)[4]].



(5a)R:OH
(5b)R:H

In addition, benzoic dimethyldithiocarbamic anhydride (2)[2] was employed as a benzoylating reagent in place of 1.



(2)

When the coumpound 2 (5 mmole) was treated with cytidine (1 mmole) in dry dimethyl sulfoxide (DMSO) (5 ml) at room temperature for 2 days, N^4-benzoylcytidine (5a) was obtained in almost quantitative yield.

In the same manner, N^4-benzoyldeoxycytidine (5b) was also obtained almost quantitatively.

In these reactions, it was found that DMSO is superior to other solvents such as pyridine and DMF.

It was found that 2 was not effective for benzoylation of cytidine 5'-phosphate. When 2 was treated with cytidine 5'-phosphate, 4a was obtained in only 15% yield.

It can be said that the reagent 1 is more suitable than 2-chloromethyl-4-nitrophenyl benzoate which was reported previously[1h].

The authors heartily thank Professor Teruaki Mukaiyama for his encouragemen and discussion throughout the investigation.

References

1) (a) F. Cramer, W. Saenger, K.H. Scheit, and J. Tennigkeit, Ann., 679, 156 (1964); (b) Y. Mizuno, T. Itoh, and H. Tagawa, Chem.Ind., 1498(1965); (c) M. van Montagu and J. Stockx, Arch.Intern.Physiol.Biochem., 73, 158(1965); (d) K.A. Watanabe and J.J. Fox, Angew.Chem., 78, 589(1966); (e) T. Sasaki and Y. Mizuno, Chem.Pharm.Bull., 15, 894(1967); (f) L.N. Nikolenko, V.N. Nezavibat'ko, and N.S. Tolmacheva, Khimiya Prirod.Soedin, 139(1967); (g) L.N. Nikolenko, V.N. Nezavibat'ko, and M.I. Semenova, Zh.Org.Khimi, 49, 223 (1969); (h) T. Hata and T. Kurihara, Chem.Lett., 859(1973).

2) P.G. Nair and C.P. Joshusa, Tetrahedron Lett., 4785(1972).

3) G. Bulmer and F.G. Mann, J.Chem.Soc., 674(1945).

4) Paper chromatography (PPC) was performed by descending technique using Toyo Roshi No. 51 paper. The solvent systems used were: ethanol-1M ammonium acetate, pH 7.5 (5:2 v/v),(A); 1-butanol-water (86:16 v/v),(B).

5) D.H. Rammler and H.G. Khorana, J.Amer.Chem.Soc., 84, 3112(1962).

6) H. Schaller, G. Weimann, B. Lerch, and H.G. Khorana, ibid., 85, 3821(1963).

(Received October 30, 1975)